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July 13, 2003

Christopher Portier, Ph.D., Chair,
Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP)
and the Panel Members for Characterization of Atrazine Cancer Epidemiology Data
Office of Pesticide Programs (OPP; 7101C)
U.S. Environmental Protection Agency (EPA)
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Docket ID number OPP- 2003-0186

Comments by Consultants in Toxicology, Risk Assessment and Product Safety (CTRAPS) to the FIFRA SAP about the characterization of atrazine cancer epidemiology data [*Federal Register 68(104):* 32488-32490 (May 30, 2003)].

Dear Dr. Portier and Members of the Panel:

CTRAPS is a biomedical consulting firm which, among other activities, designs, conducts, and evaluates research for clients. Some of this research involves assessing the carcinogenic potential of chemical substances in the environment. So, CTRAPS has a vital interest in EPA's revision of its existing carcinogen risk assessment guideline and EPA's risk characterization policies (EPA, 1995; EPA, 1996; SPC, 2000). CTRAPS previously commented to OPP and the FIFRA SAP about atrazine (CTRAPS, 1999; CTRAPS, 2001). In addition, James D. Wilson, Ph.D., Vice-President of CTRAPS, published articles and provided comments about atrazine to OPP and to the FIFRA SAP (Wilson, 2000a; Wilson, 2000b; Wilson, 2000c; Wilson, 2001).

In summary, our two comments for the Panel are as follows:

(1) CTRAPS agrees with OPP that the available data do not support a relationship between atrazine exposure and human prostate cancer.

(2) No sound scientific basis exists to reclassify atrazine as a human carcinogen right now.

The two sections below explain the summary comments.

(1) CTRAPS agrees with OPP that the available data do not support a relationship between atrazine exposure and human prostatic cancer. Atrazine is not likely to be the primary factor in

the prostatic tumors observed in the St. Gabriel study, and a satisfactory alternative explanation exists for the observed excess tumor prevalence.

An occupational study of 2045 workers at a manufacturing facility in St. Gabriel, LA between 1985 and 1997 (21,200 person-years, median 3.8 years worked) reported 46 observed and 40 expected cases of all cancers combined [Standardized incidence ratio (SIR) = 114, CI = 83-152] (MacLennan et al., 2002). The study reported 11 workers with prostate cancer, when 6.3 were expected, also not a significant excess of cases (SIR = 175, CI = 87-312). However, more cases of prostate cancer occurred among 757 actively working company employees (5/1.3, SIR = 394, CI = 128-920) than in 1288 contract employees (6/5.0, SIR = 119, CI = 44-260).

OPP reports data from a later study of the same facility, which found six additional cases with follow-up extended through 1999 (Delzell, 2001). Thus, in the later study, the St. Gabriel plant had accumulated 17 cases of prostate cancer. Fourteen of these 17 cases occurred among regular employees, most of whom participated in a prostate specific antigen (PSA) screening program. Twelve cases of prostate cancer occurred in company employees with atrazine exposure, compared with 4.7 to 6.7 expected, depending on the comparison populations, either overall LA rates or LA industrial corridor rates, for a significant excess of 5.3 to 7.3 cases. However, this study did not have an available comparison population of workers similarly undergoing PSA screening.

The St. Gabriel study is not concordant with the best quality epidemiological data about occupational exposure to atrazine and prostatic cancer, which come from the Agricultural Health Study (AHS). The AHS examined prostate cancer incidence in a prospective cohort study of 45 pesticides which involved 55,332 male pesticide applicators (Alavanja et al., 2003). Significant associations with prostate cancer incidence related to the use of methyl bromide and the use of chlorinated pesticides by applicators more than 50 years old, not to atrazine.

In contrast, an ecological study by Mills (1998) found a significant positive correlation (0.67) between pounds of atrazine applied in each California county and prostate cancer among black persons in the same counties. Mills also observed negative correlations between pounds of atrazine applied in California counties and prostate cancer in the same counties for Hispanic, Asian or white persons. Because the study was ecological, and because the results for different subgroups diverge, the most likely explanation for the correlation between counties with more atrazine applied and counties with more prostate cancer among black persons, is random chance. Mills did not apply a correction factor for estimates of significance in correlation coefficients for the number of simultaneous correlations. However, the study involved the intersection of four racial/ethnic/skin color groups, six diseases, and six pesticides, or 144 correlations.

The use of PSA screening at the St. Gabriel site provides a satisfactory alternative explanation for the observed excess of tumor prevalence (MacLennan et al., 2002). In the published study, PSA screening led to detection of 9 of 11 cases in company employees. (Contract workers were not similarly screened.) In OPP's analysis, the PSA program led to detection of 10 of the 12 prostate cancer cases among company employees with exposure information. Staging of prostatic

cancer cases also was consistent with PSA screening explanation. Consistent with this hypothesis, workers with prostate tumors were younger and had earlier stage, localized, asymptomatic tumors. A different interpretation, that atrazine caused the increase in cases of prostate cancer, requires a belief that PSA screening is ineffective.

(2) No sound scientific basis exists to reclassify atrazine as a human carcinogen right now. EPA's risk characterization policy calls for a transparent process which generates clear, consistent and reasonable work products (EPA, 1995; SPC, 2000). OPP's documentation, availability of these documents, and public communications have provided much of the necessary transparency and clarity. The consistency and reasonableness of the risk characterization are at stake in these SAP deliberations. Risk characterization needs procedures to cope with spurious events, particularly when the kind of study, such as an epidemiology study, because of the stochastic basis of its measurements and interpretation, is expected to generate spurious results on a regular basis. Right now, one way that EPA attempts to find consistency and reasonableness in risk characterization of carcinogens is through the application of a modification of the Bradford Hill criteria (Byrd and Cothern, 2000). One of the criteria is biological plausibility.

The SAP will have to advise OPP about the relationship between the excess prostate tumors seen in the St. Gabriel work force and the neuroendocrine-related mode of action which explains mammary and pituitary gland tumors seen in female rats of certain strains, particularly Sprague-Dawley female rats. Neuroendocrine disruption is not the likely cause of the prostatic tumors observed in St. Gabriel, because this mode of action would predict a decrease in human male prostate tumors, not an increase.

CTRAPS agrees with OPP's classification of atrazine as "Not Likely to Be Carcinogenic to Humans." OPP made this classification in response to mammary and pituitary gland tumors observed in atrazine-treated female Sprague-Dawley rats. Atrazine-induced rat tumors are strain and sex specific. Atrazine does not induce mammary and pituitary gland tumors in mice, in male rats, or in female rats of several strains. The usual mode of chemical carcinogenesis is somatic cell mutation. However, negative mutagenicity studies contradict the idea that atrazine, or a metabolite of atrazine, forms DNA adducts or causes some other kind of mutagenic lesion, such as a chromosomal abnormality (OPP. 2000a). A somatic mutation mode of action also is difficult to reconcile with a highly specific sex, strain and species pattern of carcinogenesis.

Instead, strong evidence supports the idea that atrazine acts with low potency on CNS cells generating neurotransmitters (OPP, 2000b). Altered hypothalamic neurotransmitter and neuropeptide levels provide satisfactory explanations both for mammary and pituitary gland tumors in rats and for the sex and strain specificity of the tumor response in rats. However, if it applied to male humans, the mode of action in female Sprague-Dawley rats would predict a decrease in prostate tumors, not an increase. Atrazine should cause a dose-dependent reduction in testosterone secretion by testicular Leydig cells, an effect observed in atrazine-treated male Sprague-Dawley rats (Trentacoste et al., 2001). Thus, the hypothesis that atrazine increases the risk of prostate cancer lacks biological plausibility.

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Respectfully submitted,

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